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Abstract: Background: The lack of availability of evidence-based services for people exposed to adversity globally has led to the development of psychological interventions with features that will likely make them more scalable. The evidence for the efficacy of e-mental health from high-income countries is compelling and the use of these interventions could be a way to increase the coverage of evidence-based psychological interventions in low- and middle-income countries. Step-by-Step, is a brief (5 session) intervention proposed by WHO as an innovative approach to reducing the suffering and disability associated with depression. Objective: This study aims to evaluate the effectiveness and cost-effectiveness of a locally adapted version of Step-by-Step with Syrian nationals (trial 1) and Lebanese nationals and other populations residing in Lebanon (trial 2). Methods: This Step-by-Step trial involves two parallel, two-armed randomized controlled trials (RCTs) comparing the e-intervention Step-by-Step to enhanced care as usual (ECAU) in participants with depressive symptoms and impaired functioning. The RCTs are designed and powered to detect effectiveness in two populations: Syrians in Lebanon (n=568) and other people residing in Lebanon (n=568) (Lebanese nationals and other populations resident in Lebanon). The primary outcomes are depressive symptomatology (measured by the Patient Health Questionnaire [PHQ-9]) and functioning (measured by the WHODAS 2.0). Secondary outcomes include anxiety symptoms, post-traumatic stress disorder (PTSD) symptoms, personalized measures of psychosocial problems, subjective wellbeing and economic effectiveness. Participants are mainly recruited through online advertising. Additional outreach methods will be used if required, for example through dissemination of information through partner agencies and organizations. They can access the intervention on a computer, tablet and mobile phone through a hybrid app. Step-by-Step has 5-sessions and users are guided by trained non-specialist "e-helpers" providing phone or message-based support for around 15 minutes a week. Results: The trials were funded in 2018. The study protocol was last verified 20.06.2019 (WHO ERC.0002797) and registered with ClinicalTrials.gov (NCT03720769). The trials started recruitment as of December 9th, 2019 and all data collection will likely be completed by November 2020. Conclusions: The Step-by-Step trials will provide evidence about the effectiveness of an E-mental health intervention in Lebanon. If the intervention proves to be effective, this will inform future scale up of this and similar interventions in Lebanon and in other settings across the world. Clinical Trial: NCT03720769

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¹Department of Mental Health and Substance Use World Health Organization Geneva CH

²Department of Psychology Psychopathology and Clinical Intervention University of Zurich Zurich CH

³National Mental Health Programme Ministry of Public Health of Lebanon Beirut LB

⁴Department of Education and Psychology, Division of Clinical Psychological Intervention Freie Universität Berlin Berlin DE

⁵Department of Educational and Family Studies Amsterdam Center for Learning Analytics Vrije Universiteit Amsterdam NL

⁶Department of Clinical, Neuro and Developmental Psychology Amsterdam Public Health research institute Vrije Universiteit Amsterdam NL

⁷Department of Digital Health and Innovations World Health Organization Geneva CH

⁸Country office for Lebanon World Health Organization Beirut LB

Corresponding Author:

Edith van 't Hof PhD

Department of Mental Health and Substance Use

World Health Organization

Avenue Appia 20

Geneva

CH

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Original Manuscript

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¹ Department of Mental Health and Substance Use, World Health Organization, Geneva, Switzerland.

² Department of Psychology Psychopathology and Clinical Intervention, University of Zurich, Switzerland

³ National Mental Health Programme, Ministry of Public Health of Lebanon, Beirut, Lebanon

⁴ Department of Education and Psychology, Division of Clinical Psychological Intervention, Freie Universität Berlin, Berlin, Germany

⁵ Department of Educational and Family Studies, Amsterdam Center for Learning Analytics, Vrije Universiteit, Amsterdam

⁶ Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit, Amsterdam

⁷ Department of Digital Health and Innovations, World Health Organization, Geneva, Switzerland.

⁸ Country office for Lebanon, World Health Organization, Beirut, Lebanon

Corresponding author: Edith van 't Hof, edithvanhof@gmail.com

Abstract

Background

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as of December 9th, 2019 and all data collection will likely be completed by November 2020.

Discussion

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Trial registration: ClinicalTrials.gov identifier: NCT03720769

Keywords: psychological intervention, adversity, E-mental health, Lebanon, Syrians

Introduction

Most people suffering from mental health problems do not access mental health care. It is estimated that in low- and middle-income countries the majority (76–85%) of people suffering from mental disorders receive no treatment at all [1]. This disparity is even bigger in communities exposed to adversities where the prevalence of mental health problems is higher and resources are often scarce [2]. The lack of availability of evidence-based services for people exposed to adversity globally has led to an interest in developing psychological interventions that are more likely to be scalable in low-resourced settings [3].

Lebanon has a history of political instability that has negatively impacted the development of the country. There are approximately 1.5 million Syrian refugees in Lebanon, of which 74 percent are lacking legal status [4]. The country's resources are extremely stretched, and the growing number of refugees put extra pressure on the labour market and infrastructure. The treatment gap for mental

health problems is estimated at over 90% by the National Mental Health Programme at the Ministry of Public Health (MoPH) [5]. A national epidemiological survey (involving 2,857 people in Lebanon) published before the Syrian civil war, showed that one in six people met criteria for mental disorder, with 27.0% of these “serious” [6]. Only one in nine respondents with a mental disorder had ever obtained any treatment. More recent data shows that the situation has improved, but treatment seeking still remains low, with a treatment gap of approximately 80% [7]. Affordable and accessible mental health care is very limited in Lebanon. MoPH data from 2015 show that there are 1.26 psychiatrists and 3.42 psychologists per 100,000 population and 97% of the mental health care staff works in private practice in Lebanon, which limits access to affordable care [5]. Since 2015, the MoPH in Lebanon has trained staff in more than 70 PHC centres nationwide on the assessment and management of people with mental health conditions following World Health Organization (WHO) mental health gap action programme (mhGAP) guidelines [8]. With a high prevalence of mental health problems in both refugees and the Lebanese host community, and limited resources, there is a considerable need to scale up mental health and psychosocial support services in Lebanon.

E-mental health, which is the use of electronic devices to provide mental health interventions, could be a way to increase the coverage of evidence-based psychological interventions in a sustainable manner. In high income countries, guided online self-help programmes have been found to be as effective as the same interventions provided face-to-face [9-11]. In addition, such programmes have been shown to reduce symptoms of mental disorders in routine care [12]. With ample evidence supporting the use of e-mental health, a number of countries' now include e-mental health in their national mental health strategies and treatment guidelines (e.g., the Netherlands, the United Kingdom, Australia, New Zealand, Scandinavian countries [13] and Lebanon [5, 14]. In Lebanon, a substantial proportion of the population has access to mobile phones (92%) and the internet (78%) [15]. This suggests that many Lebanese have the means to access an e-health intervention, with this percentage likely to rise in the coming years [16]. The adult literacy rate is 88%, with youth literacy at 96% [17]. Syrians in Lebanon also have access to smartphones and the internet, with 80% reporting access at the household level (e.g. one phone per household)[18]. The potential of digital interventions is that they can reach more people than more in-person interventions and high drop-out rates are common.

Step-by-Step is a brief (5 session) e-mental health intervention for depression proposed by WHO as an innovative approach to reducing the suffering and disability associated with mental health issues [19]. It has been carefully designed and comprehensively adapted for use in Lebanon (including for refugees residing in Lebanon [20]). Step-by-Step is guided by trained non-specialist “e-helpers”

providing phone or message-based support to Step-by-Step users for around 15 minutes a week. It can also be used with different guidance models including no contact or contact on demand.

This paper describes the protocol for two randomized controlled trials (RCTs) of Step-by-Step in Lebanon. The study protocol has been informed by previous formative work [20, 21], an uncontrolled pilot [14] and a feasibility RCT showed the acceptability and feasibility of Step-by-Step [22]. The feasibility RCT was not powered to evaluate treatment effects, although estimates for complete cases at post-assessment showed a significant reduction of depressive symptoms, anxiety, posttraumatic stress and an improvement of functioning and well-being. The intention-to-treat analysis showed a marginally non-significant effect on functioning and a trend into the expected direction for the other measures. These results indicate the importance of evaluating the effectiveness of Step-by-Step in fully powered RCTs [22]. Because of the specific needs of different populations, the research effort is evaluating Step-by-Step with Syrians in Lebanon and other populations residing in Lebanon (e.g. Lebanese and other refugee groups). Given the potentially substantial differences in experiences of migration and recent trauma between these two groups and that separate funding was received for the evaluations of SbS in these two groups, two RCTs were planned. The RCTs are powered to evaluate effectiveness and cost-effectiveness of Step-by-Step in the two populations. As the two RCTs use the same infrastructure and protocol this paper describes both of them at the same time.

Methods

Objectives

This study aims to evaluate the effectiveness and cost-effectiveness of a locally adapted version of Step-by-Step in people residing in Lebanon, including Lebanese nationals, Syrian displaced people and other populations resident in Lebanon. The RCTs will compare the e-intervention Step-by-Step to enhanced care as usual (ECAU) in participants with depressive symptoms and impaired functioning. One RCT will involve Syrian populations in Lebanon and the other will involve other people residing in Lebanon.

Design and setting

The study is designed as two pragmatic parallel two-arm RCTs. Participant level outcomes will be measured at three time points; baseline (t0), post-treatment (t1) and follow-up (t2). Post-treatment

(t1) has been set at 8 weeks after baseline (t0) and follow-up (t2) at 3 months after post-treatment (t1), so five months after baseline (t0). Post-treatment is the primary outcome for the study. In both RCTs Step-by-Step will be compared to ECAU. In one RCT with Syrians in Lebanon (hereafter called 'Syrian' group) and in the other RCT with other populations residing in Lebanon (e.g. Lebanese and other refugee groups, hereafter called 'Lebanese and others' group). Both RCTs use the exact same infrastructure and the study is powered to detect effectiveness for both groups.

The primary hypothesis is that at post-treatment (8 weeks after baseline), in both the 'Syrian' and 'Lebanese and other' group, people receiving Step-by-Step will have less severe depressive symptoms (measured by the Patient Health Questionnaire [PHQ-9]) and higher levels of functioning (measured on WHODAS 2.0) compared to people receiving ECAU. The secondary hypothesis is that people receiving Step-by-Step will report fewer anxiety symptoms, posttraumatic stress disorder (PTSD) symptoms, personally identified psychosocial problems, and higher levels of subjective wellbeing. In addition, we hypothesise that offering Step-by-Step is more cost effective than ECAU.

Study arms

Step-by-Step intervention

Step-by-Step is brief (5-sessions) and has been designed to primarily address depressive symptoms [19]. Behavioural activation is the main active therapeutic agent in the intervention, as it is easy for users to engage with, has a very strong evidence base for depression [23, 24], and can easily be adapted to a minimally guided, internet delivery model [25]. The intervention follows a narrative story-based approach to convey information together with illustrations and weekly exercises. The narrative and exercises aim to increase behavioural activation, including pleasurable activities and social support. Additional strategies to support this include: two stress management techniques; a gratitude and positive self-talk exercise; mood tracking where a user is regularly prompted to enter their mood on a graphical five-point Likert scale. The story and its illustrations have been adapted to the local context, considering linguistic and cultural nuances within the different populations residing in Lebanon (broadly speaking, Lebanese, Syrian and Palestinian people). Separate papers have been published with more information about the concept behind Step-by-Step [19] and about the adaptation process for Lebanon [20].

In brief, the Step-by-Step narrative has a male and female version with two versions per gender; one

broadly for married people with children and one for younger single people without children. The text content is slightly adapted across these versions, but the therapeutic content stays the same. There are also different versions of the illustrations allowing people the choice between a bearded or un-bearded character or a character with or without a headscarf. This accounts for gender differences and provides broad tailoring for the main cultural groups of target users. The language used in the intervention is simple so it can easily be understood, and the intervention has audio-recordings of all the written text that can be played by people with lower levels of literacy. More information on the intervention can be found in Carswell et al (2018) [19] and Abi Ramia et al (2018) [20].

The intervention was first developed as an internet intervention and then developed into an iOS and Android app [21] that can be used mostly offline on mobile devices and into a Web App that can be accessed via web browser. These RCTs are testing Step-by-Step as a guided self-help intervention in which Step-by-Step is supported by trained non-specialist research assistants (called “e-helpers”), who have weekly phone or message-based contact approximately 15 minutes long with users to provide support and guidance. E-helpers have an undergraduate degree in psychology or social work and work under the regular supervision of trained mental health practitioners. They will receive a 4,5-day training in the research protocols and the intervention itself, including how to guide users in implementing the techniques learned in the intervention and how to use the online system. They are supported in this by a manual and clear session by session outlines for the support contacts. Knowledge and therapeutic skills covered in the e-helper training include: working with people with depression and other mental health problems, identifying and dealing with crisis situations, and responding to adverse events. E-helpers need to pass a competency test to be involved in the RCTs. During the trials, fidelity checks will be conducted to ensure adherence to the guidance protocol using a treatment fidelity checklist. The supervisor and the study coordinator will supervise up to 5% of the responsive support contacts through listening in to calls and reviewing messages.

Weekly clinical supervision will be provided to e-helpers by a clinical supervisor from MoPH with a good understanding of the Step-by-Step intervention and research project. Clinical supervision will ensure fidelity of the guidance provided and involves discussion of difficulties encountered in supporting the users of the intervention, as well as self-care for e-helpers. In addition, weekly supervision on research processes will be provided by the local study coordinator

Enhanced Care as Usual (ECAU)

ECAU will consist of basic psychoeducation and referral to evidence-based care. If randomised into the ECAU condition, users will first receive basic psychoeducation on depression via the hybrid app.

The text for the psycho-educational messages is taken from the first session of Step-by-Step to make sure the information provided is identical. After receiving the psycho-education, ECAU users will receive a list of selected primary health care (PHC) facilities with staff trained in the mental health gap action programme (mhGAP) where they can seek evidence-based care as usual consisting of assessment and pharmacological and/or psychosocial management of mental health conditions according to mhGAP [8] .

Randomization

Upon completion of the baseline assessment, participants will be randomized to either the intervention or ECAU, using a 1:1 allocation ratio. The randomization is handled by an algorithm for permuted block randomization that is built into the app and not accessible to the research team. The algorithm generates a random sequence of blocks with varying length. In each block the number of seats for both groups is even and the order is fully random.

Sample size calculation

A recent meta-analysis of depression treatments in low- and middle-income countries has been conducted with 32 RCTs, looking at different intervention types, formats (e.g. guided self-help, group therapy), and comparators (e.g. waitlist, treatment as usual) [26]. An effect size of 0.73 (Hedges' g) was found for symptoms of depression. Moreover, a recent meta-analysis of Internet- and mobile-based interventions for the treatment of depression in high-income countries, including 19 RCTs, showed an effect size of 0.90 (Hedges' g) when comparing these treatments with waitlist condition [27, 28]. Despite these relatively high effect sizes reported in literature, the power calculation for these RCTs was completed for a more conservative (but still clinically significant) effect size of Cohen's $d = 0.5$.

Assuming one primary outcome, a power of 90% and an alpha of 0.05, the two RCTs needs 85 participants in each of the 2 arms, in order to be able to detect a moderate effect size of 0.5. For the two primary outcomes considered, this yields a complete power (i.e. the probability to detect statistically significant effects of at least 0.5 on both outcomes, given that both effects truly exist) ranging from 81% (independence between outcomes) to 90% (perfect correlation between outcomes). For individual power (i.e. the probability of detecting an effect of 0.5 or larger for a particular outcome, given that the specific effect truly exists), applying a Bonferroni multiple testing procedure (MTP) to control the family-wise error rate (FWER) at -or below- an alpha of 0.05 yields an individual power of 84% [29]. We note that Bonferroni is overly conservative in the case of

dependency between outcomes, such that the true FWER is likely to be somewhat below 5% [29]. In our feasibility RCT [30] we found a dropout rate of 70% which is consistent with other e-mental health studies [31, 32]. Accounting for a dropout rate of 70%, $(2 \times 85) / (1 - 0.70) = 568$ Syrian displaced people and 568 other people residing in Lebanon will thus be recruited for the trials such that 85 are estimated to complete the intervention (complete 4 of 5 sessions) in the intervention arms of each trial.

Participants

Any person aged over 18, residing in Lebanon, who can understand and speak Arabic or English, and has access to an internet connected device is eligible to participate. Additional inclusion criteria are: 1) scoring 10 or above on the PHQ-9 [33] and 2) scoring above 16 on the WHO Disability Assessment Schedule for functional impairment [34]. Minors (under the age of 18) and people who have plans to end their life (as indicated by an answer of “yes” on an additional screening question - “In the past month, have you had serious thoughts or a plan to end your life?”) will be excluded from the study. Participants who answer “yes” to this additional screening question will be considered at imminent risk of suicide and will receive an on-screen message explaining that they may need additional mental health support with advice to go to an emergency room or call the national suicide hotline (Embrace Lifeline) established by the MoPH for suicide prevention. They will also be presented a list of facilities providing mhGAP care, encouraged to seek help and provided with additional self-care tips.

Procedures

The research procedures can be found in figure 1. Recruitment of participants will be conducted through online advertising, primarily a social media campaign comprising of posts including videos, animations, gifs and images. The posts will be disseminated through multiple channels, including the social media platforms of the National Mental Health Programme (NMHP) at the MoPH in Lebanon. The campaign will be conducted by a professional communication company in close collaboration with the NMHP team. Additional outreach methods will be used where required, for example, dissemination of posts through partner agencies and organizations.

People interested can access the website or download the native iOS/Android App version of Step-by-Step. They will enter the onboarding section of the app with information about Step-by-Step and the research project. The onboarding section of the app also contains an animation which explains the most important points in a short video.

People will apply to join the study by following on screen instructions in the app/website. After giving consent they will be asked to create an account. They will be asked to indicate their age and complete an initial self-screening measure (PHQ-9, WHODAS 2.0 and additional suicide screening question). If an individual meets the inclusion criteria, they are asked to complete the study baseline questionnaires. Upon completion of the baseline assessment they will be randomized to either the intervention or ECAU, using a 1:1 allocation ratio in the programme. If the individual does not score over the clinical cut-off on the PHQ-9, a box will appear saying that the intervention may not be a good fit for them and suggesting they seek support from a health care worker.

At sign-up, users will be asked to choose at least one method of follow-up contact from phone call, e-mail, or SMS for reminders of the assessments. People allocated to Step-by-Step are also asked to confirm their contact preferences for regular support from e-helpers. Applicants will be able to contact a member of the study team throughout the self-screening and recruitment process for free, using telephone or messaging services. On completion of enrolment upon sign-up research staff will either call or send a message to users in the control group (depending on their preferred contact option) to thank them for their participation in the study and to remind them of the format of the study (e.g. post- and follow-up questionnaires). Users who access the study through the app (i.e., not via web-browser) will be asked if they would like to receive notifications on their smartphone. These notifications will cover: a) assessments due (both conditions); b) new sessions available (only intervention condition); c) monthly automated messages to remind users of the upcoming assessments and to thank them for their ongoing participation in the study assessments (both conditions); and mood tracking (only intervention condition). Users will receive an explanation at the beginning of the study about the purpose and reasons for these notifications and can opt out of some or all of notifications at any time. If assessments are due, e-helpers will contact users (both intervention and control participants) via their preferred method of contact (phone, email etc). As remuneration users will receive \$20 phone credit for completion of all questionnaires at all time points.

Informed consent

All research participants will be asked for individual electronic informed consent. A known challenge in informed consent procedures in resource-limited settings is applicants feeling pressure to answer assessment questions because they see the research process as a route to access services and other resources. This problem is expected to be diminished by the fact that the recruitment will mainly be done through social media instead of face to face. All participants will go to the site on their own

accord and be provided with detailed information at the start intervention. Full information on the study will be provided in a video animation in the local language as part of the consent form before requesting consent as, also available both written and as audio file. Applicants will receive information about what they can expect (i.e., group allocation, assessments, reminders, etc.). In addition, they will be reminded that they are free to withdraw at any time, and that non-participation will not affect in any way their access to usual health care.

E-helpers will receive in-depth training on the informed consent process and will be working in accordance with this protocol. All data and informed consent will be collected online, with telephone or messaging support from e-helpers if necessary. Respondents who decide to participate will be asked to electronically sign the consent form.

Outcome measures

Primary outcomes

The primary outcomes are levels of depressive symptoms measured by the Primary Health Questionnaire (PHQ-9)[33] and levels of functioning measured by the WHODAS 2.0 [34] at post-treatment (8 weeks after baseline).

The PHQ-9 is a well-known 9-item instrument measuring presence and severity of depression [33]. As a severity measure, the PHQ-9 score may range from 0 to 27, since each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day). The PHQ-9 has been validated in the Lebanese population with a cut-off score of 10 or above indicating moderate depression [35]. The PHQ-9 is now worldwide one of the main outcome measures that is used in research on psychological interventions and has been chosen as one of the core metrics for research on psychological interventions, that should be included in all studies on psychological interventions for depression and distress, funded by the Wellcome Trust, the NIMH and other major funders [36].

The WHODAS 2.0 is a generic assessment instrument assessing health and disability [34]. It is used across all diseases, including mental, neurological and substance use disorders and in many global regions. It is simple to administer, applicable across cultures and can be used in all adult populations. WHODAS 2.0 covers six domains (cognition, mobility, self-care, getting along, life activities, participation). It assesses difficulties people have across these domains during the last 30 days. Difficulties are scored as none, mild, moderate, severe, or extreme.

Secondary outcomes

Secondary outcomes include levels of subjective well-being (WHO-5)[37]; levels of anxiety

symptoms(GAD-7)[38]; and levels of PTSD symptoms (PCL-5)[39]. In addition, subjective problems are assessed using the Psychological Outcomes Profile Instrument (PSYCHLOPS)[40]. Satisfaction will be assessed using the Client Satisfaction Questionnaire (CSQ), three items version [41]; and service utilization will be measured with an adapted version of the CSRI [42].

Please see Figure 2 for an overview of the different measures on different time-points.

The WHO-5 Wellbeing Index is a 5-item questionnaire measuring current psychological wellbeing and quality of life, rather than psychopathology [37]. Scores range from 0-25. The scale has demonstrated sensitivity to change in wellbeing and is available in multiple languages.

The GAD-7 is a seven item self-report questionnaire for generalised anxiety disorder widely used in primary and specialist care as an indicator of anxiety symptoms [38]. It consists of Likert scale questions including items on nervousness, anxiety, restlessness and fear. It is being included in this study as a means to investigate whether the intervention, which includes a stress reduction exercise and cognitive coping strategies, may reduce comorbid symptoms of anxiety. The GAD-7 has been validated in the Lebanese population [35].

PTSD symptoms during the past week will be measured using the abbreviated eight-item version of the PTSD Checklist for DSM-5 (PCL-5)[39]. Items are rated on a five-point scale from 1 to 5 and add up to a total severity score of 30. The previous short version of the PCL (PCL-6)[43] that was based on the diagnostic criteria of DSM-IV, has shown good psychometric properties and has been tested in diverse cultural settings, including Lebanon [44].

The Psychological Outcome Profiles instrument (PSYCHLOPS) [17] is a person-centred outcome measure consisting of four questions across three domains: problems (2 questions), functioning (1 question) and wellbeing (1 question). Participants are asked to indicate self-identified problems. Responses are scored on an ordinal six-point scale producing a maximum score of 20 (5 points per question). The pre- and post-intervention versions of PSYCHLOPS consist of the same four questions but the post-therapy version adds an overall evaluation question (determining self-rated outcome ranging from “much better” to “much worse”). PSYCHLOPS has been validated in primary care populations across several countries [20, 21]. It is currently used in WHO studies in Pakistan, Kenya and Uganda.

The CSQ [41] is an easily scored and administered eight item measure that is designed to measure client satisfaction with mental health services. It includes an additional free response field as well as

the eight questions that are scored on a Likert scale. To decrease questionnaire burden this study used the 3 item version of the CSQ [45] .

The CSRI was developed for the collection of data on service utilization and related characteristics of people with mental disorders, as the basis for calculating the costs of care for mental health cost-effectiveness research [42]. The CSRI was adapted for online use within a large EU funded programme, the STRENGTHS programme [21], further adapted by the team for use in Lebanon and pilot tested in the feasibility RCT [22].

During the course of the intervention, the PHQ-4 [46] will be used to monitor depressive symptoms on a weekly basis regardless of progress in the sessions. The four-items version has shown good psychometric properties and the Arabic version was validated among Syrian displaced people in Germany [46, 47].

Data on socio-demographic information (sex, age, education, marital status and work status) will be collected through questions A1-A5 of the 12 item self-report version of the WHODAS 2.0. In addition, users will be asked where they heard about the study.

Data management

Most data will be collected electronically in the app and all electronic data will be stored on password-protected computers. The data collected through computers or devices will be downloaded from the platform and migrated into a data-analysis software programme. Hardcopies of data from the study (for example from qualitative interviews and supervision notes) will be safely stored in locked cabinets. No personal data will be used in publications or presentations. The accuracy of data storage and output will be monitored bi-weekly by an external person.

Because of the nature of this innovative intervention and the data being collected online, considerable emphasis has been given to privacy and security of client data. Programming of the iOS/Android App and web versions is being managed by Freie Universität Berlin. The intervention software and all procedures involving the software will be developed in compliance with the EU General Data Protection Regulation (GDPR).

Data analyses plan

Statistical analyses

For the two RCTs both intention-to-treat analysis (including all randomized participants) and completers' analyses (per protocol, PP) will be carried out. First, the mean difference between the two treatment arms at baseline, post-intervention, and three-month follow-up is determined. Then, the treatment effect is estimated based on intention-to-treat (ITT), using regression estimation models with the principal predictor being treatment assignment status. Missing outcome observations for participants are imputed using multiple imputation exploiting pre-scores and a set of pre-specified background characteristics (gender, age, education, and severity of symptoms). Given that there are two primary outcomes of interest, we impute using multivariate normal regression using an iterative Markov Chain Monte Carlo (MCMC) method based on initial treatment assignment. The aforementioned pre-specified covariates and baseline measurement of primary endpoint are added to the baseline model for improved precision. Potential bias concerns as a result of non-random missing outcome observations are addressed by estimating Lee bounds. Then, 95% confidence intervals are constructed, both for the regression-generated point estimates and Lee (2009) bounds interval estimates. To further tighten confidence interval bounds in the context of differential and potentially non-random attrition between treatment arms, Random Forest Lee Bounds (RFLB) are estimated (using the approach in Cornelisz et al., 2019)[48].

These treatment effect analyses are performed for both primary outcome measures PHQ-9 and WHODAS 2.0. Concerns of multiple testing error are addressed by maintaining an experiment-wise type I error of 5%. In order to address potential heterogeneity, treatment effects are estimated for sub-groups (e.g. based on pre-scores). Finally, average treatment effects on the treated (ATT) are estimated treatment and corresponding measures of clinically meaningful change and numbers needed to treat (using the approach in Furukuwa et al., 2011) are explored.

In addition, the same analyses will be carried out for analysing clinical outcomes measured at each assessment time: anxiety (GAD-7), well-being (WHO5), posttraumatic stress reactions (PCL-5, eight-items version) and self-identified symptoms (PSYCHLOPS).

The health economic evaluation will be conducted from the perspective of the healthcare system to determine the difference in costs over the difference in outcomes in the intervention arm as compared to the ECAU condition.

Costs include intervention cost (e.g. costs for hosting and maintaining the intervention, costs for

e-helpers), plus healthcare costs (e.g. participants' service use as assessed with the adapted CSRI). In addition, it will be attempted to compute costs stemming from productivity losses owing to absenteeism and presenteeism (work cut back). Costs will be expressed in international dollars for the reference year 2019.

In the health-economic evaluation, the central outcome will be treatment response defined as a pre-post symptom reduction of at least 50% on the PHQ with PHQ post-test scores below the cut-off of 10, thus indicated a clinically significant reduction in depressive symptoms. Treatment response will be defined in a similar way for WHODAS 2.0.

Costs, C, and effects, E, will be combined in the incremental cost-effectiveness ratio, ICER, defined as $(C_1 - C_0) / (E_1 - E_0)$, where subscripts 1 and 0 refer to the intervention and ECAU conditions, respectively. The ICER can be interpreted as the additional cost per treatment responder.

Stochastic uncertainty in the ICER will be captured as a scatter of simulated ICERs over the ICER-plane using 2500 bootstraps. For decision-making purposes an ICER acceptability curve will be plotted indicating the likelihood that the intervention can be regarded as more cost-effective than the ECAU condition given a range of willingness to pay ceilings. Finally, sensitivity analyses will be directed at uncertainty in the main cost-drivers. The CHEERS guideline [49] will be followed when reporting the cost-effectiveness analysis.

Qualitative evaluation

To evaluate satisfaction with Step-by-Step, barriers and facilitators to adherence, and relevant information for scale-up, semi-structured interviews will be conducted with a subsample of Step-by-Step participants (including both completers as well as non-completers); control arm participants; e-helpers; supervisors and other key informants. Up to 10 people per group will be interviewed. This number is based on previous experience of the number of participants needed to reach saturation. Data will be analysed thematically. In addition, as part of process monitoring, a sample of session notes from e-helper records of their contacts with clients, as well as supervision records, will be reviewed and analysed.

Informed consent will be reconfirmed from all participants immediately prior to interviews and the interviews will take place face to face or over phone by trained interviewers. Interviewers will be using a draft semi-structured interview guide with key questions that are identified for exploration, with additional prompt questions to fully explore each question in depth. Key areas that are explored include the general experience of using Step-by-Step, acceptability, feasibility, user satisfaction and

perceived effectiveness. Interviews will be conducted no longer than 4 weeks after the final outcome assessments and are expected to last no longer than one hour.

Qualitative data analyses

The qualitative data collected from key informant interviews and notes during the process evaluation will be analysed thematically. The transcribed and translated data will be coded in NVivo [50] by multiple raters, and inter-rater reliability will be calculated using Kappa scores. Qualitative data will be analysed using thematic analysis and triangulation.

Ethical considerations

The intervention is based on evidence-based therapeutic techniques and it is unlikely that distress will increase because of participation in the programme. E-helpers will have access to the weekly depression scores (measured with the PHQ-4) of the participants and can therefore monitor distress levels over the course of the intervention. Participants who show symptom worsening (i.e., a change in category from mild to moderate or moderate to severe) will be automatically flagged by the system. All involved research staff will be trained in communication skills, providing support, responding to distress and procedures for adverse events including referral procedures.

All adverse events (AE) and serious adverse events (SAE) reported spontaneously by the participant or identified through study measures at any time will be recorded by the e-helpers. They will then notify the research coordinator and clinical supervisor for immediate follow-up action. All AEs will be followed up by the e-helper and the clinical supervisor on a regular basis. If, during self-screening or treatment, an adverse event should occur (e.g. the participant discloses plans to end their life or there is a serious protection concern requiring assistance), e-helpers will assist the users by following protocols that are based on local pathways and laws in Lebanon. Any AEs and SAEs along with actions taken will be documented and reported to the local ethical review committee ERC. SAEs will be reported within 24 hours (on working days) and AEs within 2 business days. The local ERC will review any SAEs as soon as possible and any AEs each month. They will determine any appropriate action in respect of ongoing study conduct. All SAEs will be reported to WHO ERC.

Ethical approval has been received locally from the Saint-Joseph's University (USJ) in Beirut (Protocol: CEHDF862) and by the WHO Ethical Review Committee (Version 7; Protocol ID: ERC.0002797).

Results

The trials were funded in 2018. The study protocol (version 7) was last verified 20.06.2019 (WHO ERC.0002797) and registered with ClinicalTrials.gov (NCT03720769). The trials started recruitment as of December 9th, 2019 and all data collection will likely be completed by November 2020.

Discussion

Formative work [19-21], an open pilot [14] and a feasibility RCT [30] preceded and informed the above described study protocol for RCTs to evaluate the effectiveness and cost-effectiveness of Step-by-Step in Lebanon. The RCTs will contribute to the evidence-base for the potential of guided psychological self-help using task-shifting in low- and middle-income countries [3]. It will also contribute to the growing evidence-base for the potential of digital interventions to reach broader populations with evidence-based care [51-53] and will address a gap in the evidence base in low- and middle-income countries [54].

Step-by-Step is an innovative approach to reducing the suffering and disability associated with psychological distress in a middle-income country and after testing, WHO aims to release the intervention with adaptation and implementation guidance to use in other settings. However, merely testing the effectiveness of the intervention and releasing it as a public good will not be enough to ensure the intervention will reach people that need help and can benefit from it. After successfully testing the effectiveness of Step-by-Step in RCTs, a next step would be to study ways to implement the intervention outside of a research context and identify sustainable implementation models that will support scale-up of this intervention or similar interventions in Lebanon and other countries.

Trial status

The trials will start recruiting as of December 9th, 2019 and will likely be completed by November 2020. The study protocol (version 7) was last verified 20.06.2019 (ERC.0002797). Subsequent protocol modifications will be reported to funders, IRBs, and registered with ClinicalTrials.gov.

Abbreviations:

AE	Adverse Event
ECAU	Enhanced Care As Usual
FGD	Focus Group Discussion
ICER	incremental cost-effectiveness ratio

MoPH	Ministry of Public Health
mhGAP	mental health Gap Action Programme
PHQ	Patient Health Questionnaire
PTSD	Posttraumatic stress disorder
RCT	Randomized controlled trial
SAE	Serious Adverse Event
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Scale

Declarations

Ethical approval and consent to participate

Ethical approval has been received from the Saint-Joseph's University (USJ) in Beirut (Protocol: CEHDF862) and by the WHO Ethical Review Committee (Version 7; Protocol ID: ERC.0002797). Informed consent will be obtained from all study participants.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable to this article as no datasets were generated or analysed during the development of this study protocol. The above protocol includes details on planned data availability and materials generated from this study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

All authors contributed to the development of the protocol. EvH led the drafting of the manuscript. All authors were involved in the development of the study protocol submitted for ethical approval. IC and CvK developed the statistical analysis and FS the cost-effectiveness analysis. The manuscript has been reviewed and commented on by EH, JAR, KC, MvO, RC, MHS, SB, PC, EZ, FS, IC, CvK and PN. All authors have reviewed and approved the final version of the manuscript.

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The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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Supplementary Files